REMARKS

Summary of the Office Action

Claims 1-34 are pending in this application, of which claims 1-29 are withdrawn, and claims 30-34 are under examination. Claims 30-34 are rejected as indefinite under 35 U.S.C. § 112, second paragraph, and claims 30, 31, 33, and 34 are rejected as anticipated under 35 U.S.C. §§ 102(a) and 102(b). In addition, the specification and claims are objected to for informalities.

Summary of the Amendments

The specification and claims 30 and 33 are amended herein to overcome objections and to more distinctly claim the invention. Support for the amendments can be found in the specification and in the original claim language, as set forth below. It is believed that no new matter is added by these amendments.

Informalities

A. Objection to the Specification (Priority Claim)

The Office Action states that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), because an application for which benefit of an earlier application is desired must contain a specific reference to the prior application in the first sentence of the specification (37 CFR 1.78). That is, in this case, specific reference should be made to Provisional Application 60/085,556.

In response to the objection, the specification is amended herein to insert the appropriate priority claim to Provisional Application 60/085,556. Support for this amendment is found in the "Priority Data" section of the cover page of International Application PCT/US99/10619, from which the present U.S. National Phase application was filed under 35 U.S.C. § 371; accordingly, no new matter is added by this amendment.

In addition to the foregoing amendment, enclosed herewith is a copy (marked as Exhibit 1) of Applicants' Petition Under 37 C.F.R. § 1.78(a)(6): To Accept an Unintentionally Delayed Claim For Benefit Of Priority Under 35 U.S.C. § 119(e), which is being concurrently filed with the Office of Petitions. Applicants respectfully request that the priority claim be added to the specification and that the objection be withdrawn.

B. Objection to Claims 30 and 33

Claims 30 and 33 are objected to because they refer to non-elected claims.

In response to the objection, claim 30 is amended herein such that it no longer refers to non-elected claims 1-4. Similarly, claim 33 is amended herein such that it no longer refers to non-elected claims 18-20. Accordingly, the objection to claims 30 and 33 is overcome and can now be withdrawn.

C. Objection to the Specification (Abstract)

The Office Action states that the application does not contain an abstract of the disclosure pursuant to 37 CFR 1.72(b).

In response to the objection, the specification is amended herein to incorporate the Abstract set forth on the cover page of International Application PCT/US99/10619, from which the present U.S. national phase application was filed under 35 U.S.C § 371. As required by the Office Action, a copy of the Abstract on a separate sheet is included herewith. Support for this amendment is found in the Abstract on the cover page of PCT/US99/10619 as filed; therefore, no new matter is added by this amendment. Accordingly, the objection is overcome and can be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 30-34 are rejected as indefinite under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which

Applicants regard as the invention. The rejection has three bases, each of which is individually addressed below.

A. Meaning of the term "holoparticle"

Claims 30-34 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite, on the basis that the claims recite or encompass the term "holoparticle." According to the Office Action, the term "holoparticle" is not defined in the literature and is not defined in claims 30-34. Furthermore, the Office Action states that the claims from which claims 30-34 depend are inconsistent in their presumed definition of the term.

Although Applicants do not agree that any of the pending claims are inconsistent in their presumed definition of the term "holoparticle," claims 30 and 33 are amended herein such that they no longer contain references to previous claims. Therefore, this aspect of the rejection has been overcome and can now be withdrawn.

With regard to the assertion that the term "holoparticle" is indefinite because the term is not defined in the literature, Applicants traverse. "Words in patent claims are given their ordinary meaning in the usage of the field of the invention, unless the text of the patent makes clear that a word was used with a special meaning." *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999). As described below, the term "holoparticle" was well-known to those of ordinary skill in the art before the priority date (May 15, 1998) of the present invention; accordingly, the meaning of term "holoparticle" is clear and, therefore, not indefinite.

As described in the well known text *Harrison's Principles of Internal Medicine* (14th Edition, 1998, Fauci et al. (eds.), McGraw-Hill, New York; pages 2138-2141; Exhibit 2, enclosed herewith; "Harrison's"), high-density lipoprotein (HDL) particles are formed in plasma from the coalescence of individual phospholipid-apolipoprotein complexes. Apo AI/phospholipid complexes appear to fuse with other phospholipid vesicles containing apo AII and apo AIV to form the various types of HDL. The C apoproteins can be added to HDL after their secretion as phospholipid complexes or by transfer from triglyceride-rich lipoproteins. These small cholesterol-poor nascent HDL particles are heterogeneous in size and content and

are referred to as HDL_3. Free cholesterol is transferred from cell membranes to HDL_3 and converted to cholesteryl ester by the enzyme lecithin cholesterol acyl transferase (LCAT), which moves into the core of the particle. Formation of cholesteryl ester increases the capacity of the HDL_3 to accept more free cholesterol and enlarge to form the more buoyant class of HDL particles termed HDL_2 (Harrison's, page 2141, second column, last paragraph). It is this class of HDL particles, containing esterified cholesterol (in addition to apolipoproteins, phospholipids, and free cholesterol), that are referred to in the art as HDL "holoparticles."

For example, Fluiter et al. (*Biochem. J.* 319:471-476, 1996; Exhibit 3, enclosed herewith; "Fluiter") teaches that HDL cholesteryl ester (HDL-CE), i.e., cholesteryl esters within HDL particles, can be transferred to low density lipoprotein (LDL) and very low density lipoprotein (VLDL) by the action of the cholesteryl ester transfer protein (CETP) or delivered directly to the liver. The direct uptake of HDL-CE by the liver parenchymal cells is not coupled to holoparticle uptake. That is, studies have indicated that cholesteryl esters are taken up selectively by liver parenchymal cells, exceeding uptake of the protein moiety of HDL (Fluiter, page 471, Introduction, second half of col. 1, bridging col. 2). Thus, Fluiter employs the term "holoparticle" to refer to the complete HDL particle, i.e., an HDL particle containing cholesteryl ester.

In a second example, Panzenboeck et al. (*J. Lipid Res.* 38:239-253, 1997; Exhibit 4, enclosed herewith; "Panzenboeck") teaches that:

> Several pathways contribute to the turnover of HDL-associated cholesterol esters (HDL-CE). Besides uptake of the **whole lipoprotein particle (holoparticle uptake)**, cholesteryl ester transfer protein (CETP)-mediated transfer reactions and other receptor- and enzyme-independent lipid exchange mechanisms contribute to HDL lipid turnover.... **HDL-CEs are turned over in excess of holoparticles** and this is a result of transfer and selective uptake mechanisms.

(Panzenboeck, page 239, column 2, first full paragraph; emphases added.) Thus, Panzenboeck also employs the term "holoparticle" to refer to the complete HDL particle, i.e., an HDL particle containing cholesteryl ester.

In yet a third example, Goti et al. (*Biochem. J.* 332:57-65, 1998; Exhibit 5, enclosed herewith; "Goti") teaches that:

> In contrast with LDL-associated lipids [particularly cholesteryl esters (CEs)] are turned over by three different metabolic pathways: (i) metabolism of **intact HDL particles (holoparticle** uptake [16]); (ii) CE-transfer protein (CETP)-mediated exchange [17]; (iii) a pathway termed selective uptake [18]. 'Selective' refers to the fact that CEs are extracted from the HDL particle and internalized via scavenger receptor BI (SR-BI)-mediated mechanisms without concomitant endocytosis of the remaining HDL particle [19].

(Goti, page 57, column 2, second half of first full paragraph.) Thus, Goti also employs the term "holoparticle" to refer to the complete HDL particle, i.e., an HDL particle containing cholesteryl ester.

In view of the foregoing discussion, Applicants believe that it is clear that the word "holoparticle" was a well-understood term of art as of the priority date of the present application. Therefore, Applicants request that this aspect of the rejection of claims 30-34 under 35 U.S.C. § 112, second paragraph, be withdrawn.

B. Antecedent basis for "the" polypeptide

Claims 33 and 34 are rejected as indefinite under 35 U.S.C. § 112, second paragraph, on the basis that there is insufficient antecedent basis for the term "the polypeptide," especially in the singular, in light of the term being defined by independent claims as having several possible molecular weights, for example: 40-50 kDa, 120 kDa or 400 kDa.

In response to the rejection, claim 33 is amended herein by substitution of the phrase "a polypeptide" for "the polypeptide." In addition, claim 33 has been amended to recite a Markush

group of molecular weights for the recited polypeptide. Claim 34 depends from claim 33. Applicants believe that the foregoing amendment to claim 33 overcomes this aspect of the rejection of claims 33 and 34 as indefinite, and request that the rejection be withdrawn.

C. Definition of polypeptide by molecular weight

Claims 30-34 are rejected as indefinite under 35 U.S.C. §112, second paragraph, because they define a polypeptide by molecular weight without specifying the method by which the molecular weights were obtained. The Office Action asserts that it is not known, therefore, how pure the polypeptides are or how accurate the measurements were; however, amending the independent claims to recite a method of molecular weight measurement would be remedial.

In response to the rejection, independent claims 30 and 33 have been amended to include the phrase "as measured by SDS-PAGE under non-reducing conditions," thereby specifying the method by which the molecular weights of the recited receptors and polypeptides were determined. Support for this amendment is found, e.g., at page 4, lines 21-22 and at page 33, lines 26-27, of the specification. Applicants believe that this aspect of the rejection has been overcome and therefore request its withdrawal.

In sum, Applicants believe that all three aspects of the rejection of claims 30-34 under 35 U.S.C. § 112, second paragraph, have been overcome, and therefore request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 30, 31, 33, and 34 are rejected under 35 U.S.C. § 102(b) as being unpatentable over McKnight et al. (*J. Biol. Chem.* 267:16778-16782, 1992; "McKnight"). The Office Action states that McKnight discloses binding experiments in which specific binding of HDL ligand is measured in COS and BHK cells transfected with an HDL receptor (see Table 1). The Office Action also states that the reference discloses data that show increased expression of the HDL receptor in cells bathed in a cholesterol-rich medium, and increased specific binding as a result

(page 12135). The Office Action asserts that this reference meets the limitations of claims 30, 31, 33, and 34 of the instant application in which a method of screening for ligands can include several assays, such as binding assays or measurements of HDL receptor expression, and in which the cell type is "a cell producing a functional HDL receptor."

Applicants traverse this rejection. For a prior art reference to anticipate a claimed invention, each and every element of the claimed invention must be disclosed in that single reference. As McKnight does not disclose each and every element of claim 30, 31, 33, or 34, none of the claims are anticipated by this reference.

Claim 30, as amended, recites a method of screening a substance for the ability to modulate HDL holoparticle binding and/or internalization activity of an isolated mammalian receptor that specifically binds an HDL holoparticle. The recited receptor contains two or more subunits in various combinations, such that the smallest receptor of the present invention contains a subunit of approximately 120 kDa and a subunit of approximately 40-50 kDa, as measured by SDS-PAGE under non-reducing conditions. Thus, the recited receptor of claim 30 and claim 31 (which depends from claim 30) is at least 160-170 kDa in molecular weight. Moreover, the present application teaches that receptors of the present invention bind and internalize HDL holoparticles, and thus, are endocytotic (see specification, e.g., page 4, lines 14-15; page 7, lines 4-7; and page 28, lines 26-30).

McKnight does not teach a screening method involving a receptor of at least 160-170 kDa, containing at least two polypeptide subunits, which binds and internalizes HDL holoparticles; therefore, this reference cannot anticipate claims 30 and 31. In contrast to the present invention, McKnight discloses a single polypeptide of 110 kDa (denoted "HBP") that binds HDL (McKnight, page 12131, lines 3-7 of Introduction bridging left and right columns). Moreover, McKnight teaches that cholesterol loading experiments provide preliminary evidence that HBP is a component of a cellular pathway that facilitates removal of excess cholesterol from cells (see second half of Abstract). This is in contrast to the receptor of the present invention, which transports HDL holoparticles into cells.

Claim 33, as amended, recites a screening method similar to that of claim 30, except that the recited receptor has a molecular weight, as measured by SDS-PAGE under non-reducing conditions, of approximately 40-50 kDa, approximately 120 kDa, or approximately 400 kDa. In addition, as explained for claims 30 and 31 above, receptors of the present invention bind and internalize HDL holoparticles, and thus, are endocytotic (see specification, e.g., page 4, lines 14-15; page 7, lines 4-7; and page 28, lines 26-30), in contrast to the HDL-binding protein of McKnight. Claim 34 depends from claim 33.

As discussed above with regard to claims 30 and 31, McKnight does not anticipate claims 33 and 34 because the reference neither expressly nor inherently teaches a screening method involving a receptor of the recited molecular weights, as measured by SDS-PAGE under non-reducing conditions, wherein the receptor binds and internalizes HDL holoparticles.

In sum, McKnight does not anticipate claims 30, 31, 33, and 34. Therefore, Applicants request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 102(a)

Claims 30, 31, 33, and 34 are rejected under 35 U.S.C. § 102(a) as being unpatentable over Matsumoto et al. (*J. Biol. Chem.* 272:16778-16782, 1997; "Matsumoto"). The Office Action states that Matsumoto discloses experiments in which specific binding of HDL ligand is measured in cells transfected with the HDL receptor, which is referred to as "HB_2" in the reference (see Fig. 2). The Office Action also states that the reference discloses data on the increased expression of HB_2 after stimulation of the cells with a differentiation factor as well as the consequent increase in ligand binding (see Fig. 4). The Office Action asserts that this reference anticipates claims 30, 31, 33, and 34 of the instant application in which a method of screening for ligands can be a binding assay or a measurement of HDL receptor expression, and in which the cell type is "a cell producing a functional HDL receptor."

Applicants traverse this rejection, for the same reason that the § 102(b) rejection over McKnight was traversed in the previous section. That is, for a prior art reference to anticipate a claimed invention, each and every element of the claimed invention must be disclosed in that

single reference. Matsumoto does not disclose each and every element of claim 30, 31, 33, or 34; therefore, none of Applicants' claims are anticipated by this reference.

As discussed above, claim 30, as amended, recites a method of screening a substance for the ability to modulate HDL holoparticle binding and/or internalization activity of an isolated mammalian receptor that specifically binds an HDL holoparticle. The recited receptor contains two or more subunits in various combinations, such that the smallest receptor of the present invention contains a subunit of approximately 120 kDa and a subunit of approximately 40-50 kDa, as measured by SDS-PAGE under non-reducing conditions. Thus, the recited receptor of claims 30 and 31 (which depends from claim 30) is at least 160-170 kDa in molecular weight. Moreover, the present application teaches that receptors of the present invention bind and internalize HDL holoparticles, and thus, are endocytotic (see specification, e.g., page 4, lines 14-15; page 7, lines 4-7; and page 28, lines 26-30).

Matsumoto does not teach a screening method involving a receptor of at least 160-170 kDa, containing at least two polypeptide subunits, which binds and internalizes HDL holoparticles; therefore, the reference cannot anticipate claims 30 and 31. In contrast to the present invention, Matsumoto teaches a single polypeptide of 65 kDa (denoted "HB_2") that resembles an adhesion molecule and binds HDL (see, e.g., page 16779, column 2, paragraphs 2 and 3 of "Results"). In yet another contrast to the present invention, Matsumoto teaches that HB_2 binds HDL but does not bring about internalization of HDL. That is,

> [S]pecific binding of 125I-labeled HDL3 was increased (at saturation) approximately 2-fold in transfected HepG2 cells and by 1.8-fold in transfected COS cells compared with mock-transfected cells. **This increased binding (of HDL_3 by HB_2) however was not associated with transfer of cholesteryl esters from HDL to cells because no differences were observed in cholesteryl ester uptake between mock and transfected COS or HepG2 cells** (data not shown).

(Matsumoto, page 16779, column 2, last full paragraph; emphasis added). The reference also states that "[o]ur present studies however have demonstrated that expression of HB_2 is not

associated with selective uptake of HDL cholesteryl ester by cells, a function which has been demonstrated for another candidate HDL receptor, SR-B1" (see page 16782, column 1, end of paragraph 1.) **Thus, in direct contrast to the present invention, Matsumoto teaches that HB_2 does not have internalization activity.**

Claim 33, as amended, recites a screening method similar to that of claim 30, except that the recited receptor has a molecular weight, as measured by SDS-PAGE under non-reducing conditions, of approximately 40-50 kDa, approximately 120 kDa, or approximately 400 kDa. In addition, as explained for claims 30 and 31 above, receptors of the present invention bind and internalize HDL holoparticles, and thus, are endocytotic (see specification, e.g., page 4, lines 14-15; page 7, lines 4-7; and page 28, lines 26-30), in contrast to the HDL-binding protein of Matsumoto. Claim 34 depends from claim 33.

As discussed above with regard to claims 30 and 31, Matsumoto does not anticipate claims 33 and 34 because the reference neither expressly nor inherently teaches a screening method involving a receptor of the recited molecular weights, as measured by SDS-PAGE under non-reducing conditions, wherein the receptor binds and internalizes HDL holoparticles.

In sum, Matsumoto does not anticipate claims 30, 31, 33, and 34. Therefore, Applicants request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

CONCLUSION

In view of the above amendments and remarks, reconsideration and allowance of the pending claims is believed to be warranted and such action is respectfully requested. The Examiner is encouraged to directly contact the undersigned if this might facilitate the prosecution of this application to issuance.

A Request for a Three Month Extension of Time and Credit Card Form PTO-2038 authorizing payment in the amount of $950.00, to extend the period for response by three months to December 10, 2003, are enclosed. No additional fees are believed due. However, the Commissioner is hereby authorized to charge any deficiency or to credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Shari J. Corin, Ph.D. — Date: December 3, 2003

ABSTRACT

The present invention provides an isolated mammalian receptor which specifically binds a high density lipoprotein holoparticle, comprising a subunit of approximately 450-600 kDa molecular weight and one or more subunits selected from the group consisting of a subunit of approximately 40-50 kDa molecular weight, a subunit of approximately 120 kDa molecular weight and a subunit of approximately 400 kDa molecular weight. In addition, the present invention provides a method of screening a substance for the ability to modulate the HDL holoparticle binding and/or internalization activity of the receptor of this invention, comprising: a) contacting the substance with a cell producing a functional HDL receptor; and b) assaying the cell for a modulation of the HDL holoparticle binding and/or internalization activity of the receptor, whereby a modulation of the HDL holoparticle binding and/or internalization activity of the receptor identifies a substance with the ability to modulate the HDL holoparticle binding and/or internalization activity of the HDL receptor.